

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

Glaxo Group Limited, d/b/a GlaxoSmithKline,
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 0NN
Great Britain

Plaintiff,

v.

HON. JOHN J. DOLL
Acting Under Secretary of Commerce for Intellectual
Property and Director of the United States Patent
And Trademark Office
Office of General Counsel,
United States Patent and Trademark Office
P.O. Box 15667, Arlington, VA 22215
Madison Building East, Rm. 10B20
600 Dulany Street, Alexandria, VA 22314

Defendant.

Civil Action No.:

COMPLAINT

Plaintiff, Glaxo Group Limited, for its complaint against the Honorable John J.

Doll, states as follows:

NATURE OF THE ACTION

1. This is an action by the assignee of United States Patent No. 7,452,888 ("the '888 patent") seeking judgment, pursuant to 35 U.S.C. § 154(b)(4)(A), that the patent term adjustment for the '888 patent be changed from 372 days to at least 673 days.

2. This action arises under 35 U.S.C. § 154 and the Administrative Procedures Act, 5 U.S.C. §§ 701-706.

JURISDICTION AND VENUE

3. This Court has jurisdiction to hear this action and is authorized to issue the relief sought pursuant to 28 U.S.C. §§ 1331, 1338(a), and 1361, 35 U.S.C. § 154(b)(4)(A) and 5 U.S.C. §§ 701-706.

4. Venue is proper in this district by virtue of 35 U.S.C. § 154(b)(4)(A).

5. This Complaint is timely filed in accordance with 35 U.S.C. § 154(b)(4)(A).

THE PARTIES

6. Plaintiff Glaxo Group Limited, d/b/a GlaxoSmithKline, is a corporation organized under the laws of Great Britain, having a principal place of business at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB06 0NN, Great Britain.

7. Defendant John J. Doll is the Acting Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office (“PTO”), acting in his official capacity. The Director is the head of the agency, charged by statute with providing management supervision for the PTO and for the issuance of patents. The Director is the official responsible for determining the period of patent term adjustment under 35 U.S.C. § 154.

BACKGROUND

8. Mahmood Ahmed, Christopher Norbert Johnson, Martin C. Jones, Gregor James Macdonald, Stephen Frederick Moss, Mervyn Thompson, Charles Edward Wade, and David R. Witty are the inventors of the '888 patent, which issued on November 18, 2008, from U.S. Patent application number 10/509,078 ("the '078 application") entitled "Quinoline Derivatives and Their Use as 5-HT₆ Ligands," which was issued as the '888 patent on November 18, 2008. The '888 patent is attached as Exhibit A.

9. Plaintiff Glaxo Group Limited is the assignee of the '888 patent.

10. Section 154 of title 35 of the United States Code requires that the Director of the PTO grant a patent term adjustment in accordance with the provisions of section 154(b). Specifically, 35 U.S.C. § 154(b)(3)(D) states that "[t]he Director shall proceed to grant the patent after completion of the Director's determination of a patent term adjustment under the procedures established under this subsection, notwithstanding any appeal taken by the applicant of such determination."

11. In determining patent term adjustment, the Director is required to extend the term of a patent for a period equal to the total number of days attributable to delay by the PTO under 35 U.S.C. § 154(b)(1), as limited by any overlapping periods of delay by the PTO as specified under 35 U.S.C. § 154(b)(2)(A), any disclaimer of patent term by the applicant under 35 U.S.C. § 154(b)(2)(B), and any delay attributable to the applicant under 35 U.S.C. § 154(b)(2)(C).

12. The Director made a determination of patent term adjustment pursuant to 35 U.S.C. § 154(b)(3) and issued the '888 patent reflecting that determination.

13. 35 U.S.C. § 154(b)(4)(A) provides that “[a]n applicant dissatisfied with a determination made by the Director under paragraph (3) shall have remedy by a civil action against the Director filed in the United States District Court for the District of Columbia within 180 days after grant of the patent. Chapter 7 of Title 5 shall apply to such an action.”

CLAIM FOR RELIEF

14. The allegations of paragraphs 1-13 are incorporated in this claim for relief as if fully set forth.

15. The patent term adjustment for the ‘888 patent, as determined by the Director under 35 U.S.C. § 154(b) and indicated on the face of the ‘888 patent, is 372 days. (*See* Ex. A at 1.) The determination of this patent term adjustment should be adjusted because the PTO did not properly account for the delays that occurred before the date that was three years after the actual filing of the ‘078 application, pursuant to 35 U.S.C. § 154(b)(1)(A). The correct patent term adjustment for the ‘888 patent is at least 673 days.

16. The ‘078 application was filed on September 27, 2004 and issued as the ‘888 patent on November 18, 2008.

17. Under 35 U.S.C. § 154(b)(1)(A), the number of days attributable to PTO examination delay (“A Delay”) is 498 days.

18. Under 35 U.S.C. § 154(b)(1)(B), the number of days between the date that was three years after the actual filing date of the ‘078 application (*i.e.*, September 27,

2004) and the date on which a Request for Continued Examination ("RCE") was filed (*i.e.*, March 20, 2008) ("B Delay") is 175 days.

19. Under 35 U.S.C. § 154(b)(2)(C), the number of days of applicant delay is 126 days.

20. 35 U.S.C. 154(b)(2)(A) provides that "to the extent that periods of delay attributable to grounds specified in paragraph [b](1) overlap, the period of any adjustment ... shall not exceed the actual number of days the issuance of the patent was delayed." The overlap between the "A Delay" period and the "B Delay" period in the prosecution of the '888 patent (*i.e.*, the period of "A Delay" that occurred between April 9, 2007 and September 27, 2007) is 0 days.

21. The '888 patent is not subject to a disclaimer of term. Thus the period of patent term adjustment is not limited under 35 U.S.C. § 154(b)(2)(B).

22. Accordingly, the correct patent term adjustment under 35 U.S.C. § 154(b)(1) and (2) is the sum of the "A Delay" and "B Delay" ($498 + 175 = 673$) reduced by the number of days of applicant delay (126 days) for a net adjustment of 547 days.

23. The Director should not have treated the entire period of PTO examination delay, instead of only the period of PTO examination delay that occurred after the date that was three years after the actual filing date of the '078 application, as the period of overlap between the "A Delay" and the "B Delay." Thus, the net patent term adjustment should not have been limited under 35 U.S.C. § 154(b)(2)(A) by 498 days, rather the correct number is 0 days, and the net patent term adjustment should not have been 372 days.

24. In *Wyeth v. Dudas*, 580 F. Supp. 2d 138 (D.D.C. 2008), this Court explained the proper construction of the provisions of 35 U.S.C. § 154(b) for determining patent term adjustment. In accordance with *Wyeth*, the patent term adjustment for the '888 patent is properly determined to be 547 days, as set forth above.

25. The determination that the '888 patent is entitled to only 372 days of patent term is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law and in excess of statutory jurisdiction, authority, or limitation.

PRAYER FOR RELIEF

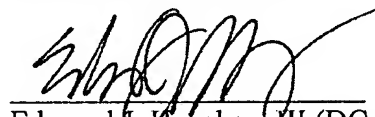
Wherefore, Plaintiff demands judgment against Defendant and respectfully requests that this Court enter Orders:

A. Changing the period of patent term adjustment for the '888 patent term from 372 days to 547 days and requiring the Director to extend the term of the '888 patent to reflect the 547 day patent term adjustment.

B. Granting such other and future relief as the nature of the case may admit or require and as may be just and equitable.

Dated: May 15, 2009

Respectfully submitted,



Edmund J. Haughey, III (DC Bar No. 462773)
FITZPATRICK, CELLA, HARPER & SCINTO
975 F Street, N.W.
Washington, DC 20004
Telephone: (202) 530-1010
Fax: (202) 530-1055
Email: ehaughey@fchs.com

Attorneys for Plaintiff
Glaxo Group Limited, d/b/a GlaxoSmithKline

Of Counsel:

Colleen Tracy, Esq.
ITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112
Telephone: (212) 218-2100
Fax: (212) 218-2200
Email: ctracy@fchs.com

Exhibit A



US007452888B2

(12) **United States Patent**
Ahmed et al.

(10) Patent No.: **US 7,452,888 B2**
(45) Date of Patent: **Nov. 18, 2008**

(54) **QUINOLINE DERIVATIVES AND THEIR USE AS 5-HT₆ LIGANDS**

(75) Inventors: **Mahmood Ahmed, Harlow (GB); Christopher Norbert Johnson, Harlow (GB); Martin C Jones, Harlow (GB); Gregor James Macdonald, Harlow (GB); Stephen Frederick Moss, Harlow (GB); Mervyn Thompson, Harlow (GB); Charles Edward Wade, Stevenage (GB); David R Witty, Harlow (GB)**

(73) Assignee: **Glaxo Group Limited, Greenford, Middlesex (GB)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 372 days.

(21) Appl. No.: **10/509,078**

(22) PCT Filed: **Mar. 25, 2003**

(86) PCT No.: **PCT/EP03/03197**

§ 371 (c)(1),
(2), (4) Date: **Sep. 27, 2004**

(87) PCT Pub. No.: **WO03/080580**

PCT Pub. Date: **Oct. 2, 2003**

(65) **Prior Publication Data**

US 2005/0124628 A1 Jun. 9, 2005

(30) **Foreign Application Priority Data**

Mar. 27, 2002 (GB) 0207289.0
Nov. 4, 2002 (GB) 0225678.2

(51) Int. Cl.
A61K 31/496 (2006.01)
C07D 215/40 (2006.01)

(52) U.S. Cl. **514/253.07; 544/363**

(58) Field of Classification Search **544/363; 514/253.07**

See application file for complete search history.

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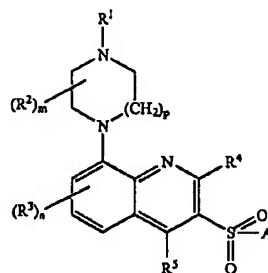
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Primary Examiner—Emily Bernhardt
(74) Attorney, Agent, or Firm—Kathryn L. Sieburth; Mary E. McCarthy; Charles M. Kinzig

(57) **ABSTRACT**

Disclosed are novel quinoline compounds of formula (I), processes for their preparation, compositions containing them and their use in the treatment of CNS disorders.



11 Claims, 3 Drawing Sheets

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Figure 1 Infrared spectrum of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I)

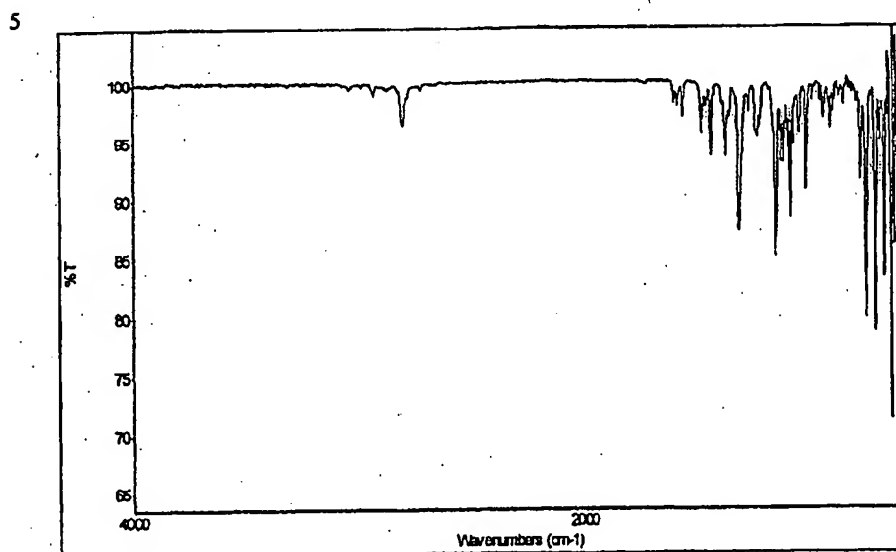
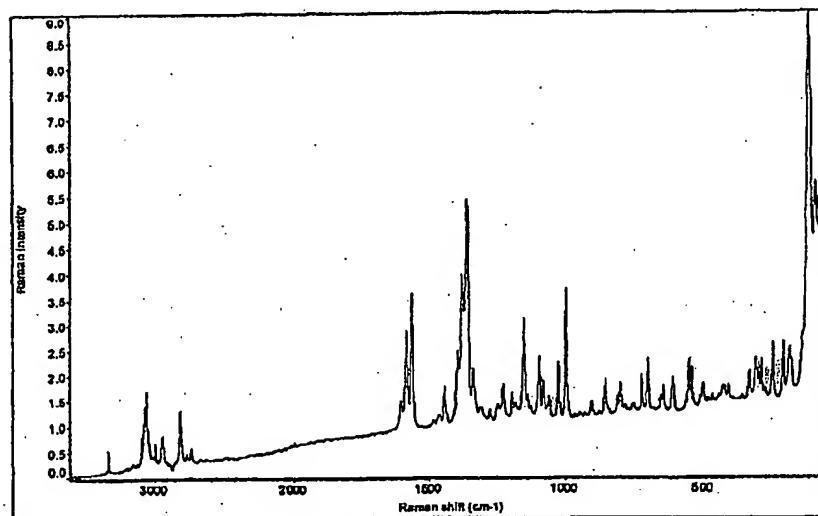


Figure 2 Raman spectrum of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I)

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Figure 3 X-Ray Powder Diffractogram of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I)

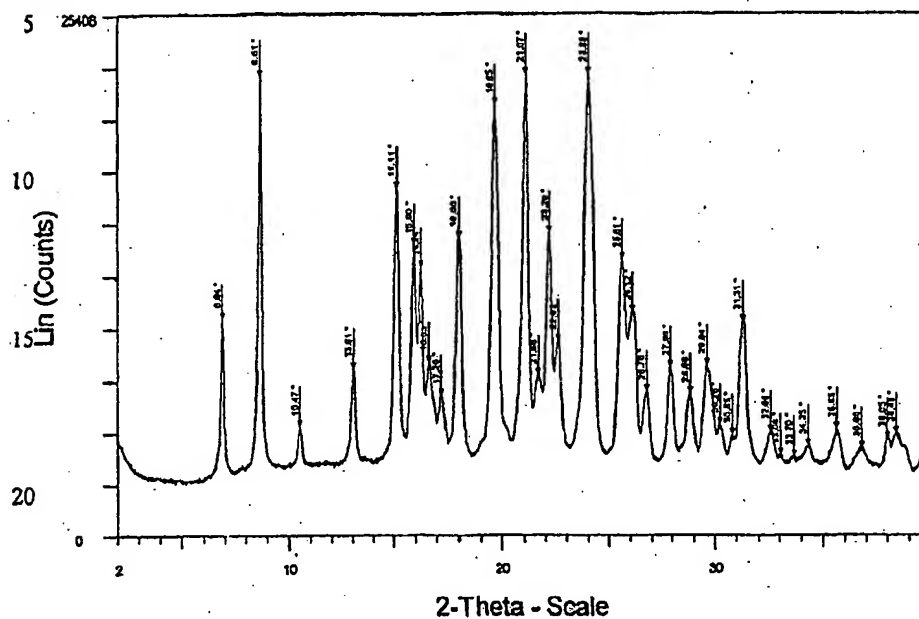
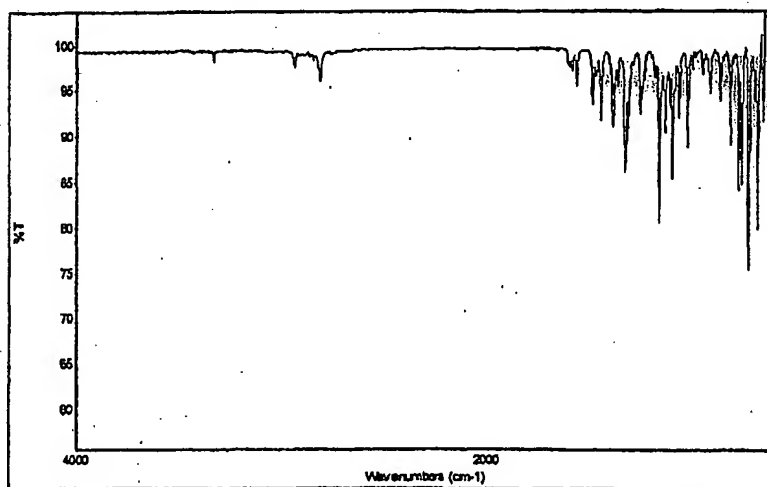


Figure 4 Infrared spectrum of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II)



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Figure 5 Raman spectrum of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II)

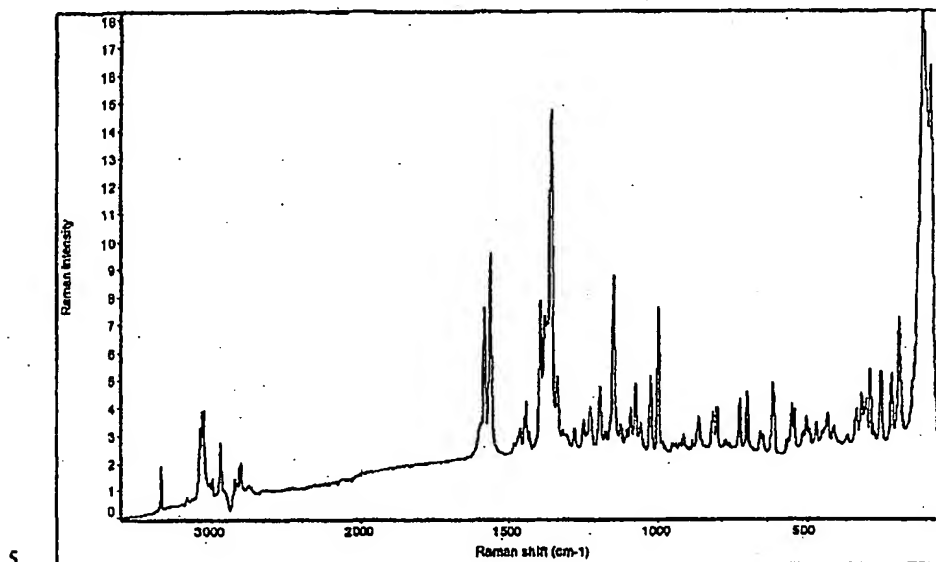
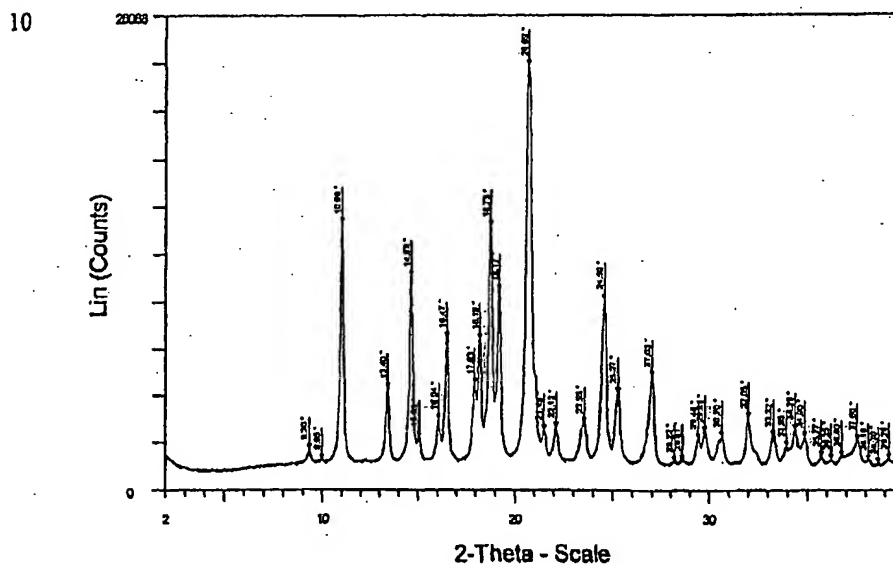


Figure 6 X-Ray Powder Diffractogram for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II)



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QUINOLINE DERIVATIVES AND THEIR USE AS 5-HT₆ LIGANDS

This application is a national stage entry under 35 U.S.C. § 371 of International Application No. PCT/EP03/03197, filed Mar. 25, 2003.

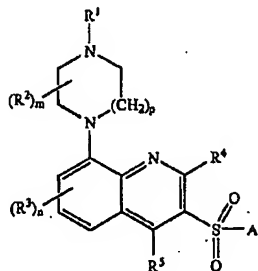
BACKGROUND OF THE INVENTION

This invention relates to novel quinoline compounds having pharmacological activity, to processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 98/27081 discloses a series of aryl sulphonamide compounds that are said to be 5-HT₆ receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders. GB-2341549, WO 99/47516 and WO 99/65906 all disclose a series of indole derivatives that are claimed to have 5-HT₆ receptor affinity. JP 02262627 (Japan Synthetic Rubber Co) describes a series of substituted quinoline derivatives useful as wavelength converting elements. WO 00/42026 (Novo Nordisk) describes a series of quinoline and quinoxaline compounds for use as GLP-1 agonists.

SUMMARY OF THE INVENTION

A structurally novel class of compounds has now been found which also possess affinity for the 5-HT₆ receptor. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

R¹ and R² independently represent hydrogen or C₁₋₆ alkyl or R¹ is linked to R² to form a group (CH₂)₂, (CH₂)₃ or (CH₂)₄;

R³, R⁴ and R⁵ independently represent hydrogen, halogen, cyano, —CF₃, —CF₃O, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl or a group —CONR⁶R⁷;

R⁶ and R⁷ independently represent hydrogen or C₁₋₆ alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

m represents an integer from 1 to 4, such that when m is an integer greater than 1, two R² groups may instead be linked to form a group CH₂, (CH₂)₂ or (CH₂)₃;

n represents an integer from 1 to 3;

p represents 1 or 2;

A represents a group —Ar¹ or —Ar²Ar³;

Ar¹, Ar² and Ar³ independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁₋₆ alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C₁₋₆ alkoxy, arylC₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkoxyC₁₋₆ alkyl, C₃₋₇ cycloalkylC₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyloxy, C₁₋₆ alkylsulfonylC₁₋₆ alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁₋₆ alkyl, C₁₋₆ alkylsulfonylamido, C₁₋₆ alkylamido, C₁₋₆ alkylsulfonylamidoC₁₋₆ alkyl, C₁₋₆ alkylamidoC₁₋₆ alkyl, arylsulfonylamido, arylcarboxamido, arylsulfonylamidoC₁₋₆ alkyl, arylcarboxamidoC₁₋₆ alkyl, aroyl, aroylC₁₋₆ alkyl, arylC₁₋₆ alkanoyl, or a group CONR⁸R⁹ or SO₂NR⁸R⁹, wherein R⁸ and R⁹ independently represent hydrogen or C₁₋₆ alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; or solvates thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the Infrared spectrum obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I).

FIG. 2 shows the Raman spectrum obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I).

FIG. 3 shows the X-Ray Powder Diffractogram obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I).

FIG. 4 shows the Infrared spectrum obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II).

FIG. 5 shows the Raman spectrum obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II).

FIG. 6 shows the X-Ray Powder Diffractogram obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II).

DETAILED DESCRIPTION OF THE INVENTION

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C₁₋₆ alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above.

It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

Preferably, R¹ represents hydrogen, methyl, ethyl, isopropyl, isobutyl or 2,2-dimethylpropyl. More preferably, R¹ represents

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resents hydrogen or methyl, especially hydrogen. Preferably R^2 represents hydrogen, methyl (eg. 3-methyl, 2-methyl, 3,3-dimethyl or 2,5-dimethyl) or is linked to R^1 to form a $(CH_2)_3$ group. More preferably, R^2 represents hydrogen or methyl (eg. 3-methyl), especially hydrogen.

Preferably R^3 represents hydrogen, methyl (eg. 6-methyl) or halogen (eg. 7-chloro). More preferably, R^3 represents hydrogen.

Preferably R^4 and R^5 independently represent hydrogen or methyl, especially hydrogen. Preferably n represents 1.

Preferably, m and p independently represent 1 or 2, more preferably m and p both represent 1.

In one preferred embodiment, m represents 2 and both R^2 groups are linked to form a CH_2 group linking C-2 and C-5 of the piperazine ring.

When A represents a group $-Ar^1$, Ar^1 preferably represents optionally substituted phenyl or pyridyl, more preferably phenyl optionally substituted with halogen (eg. chlorine, fluorine or bromine), cyano, trifluoromethyl or trifluoromethoxy. Particularly preferred Ar^1 is unsubstituted phenyl or phenyl substituted by halogen (eg. 2-chloro, 3-chloro, 4-chloro, 2-fluoro, 3-fluoro, 4-fluoro or 4-bromo), C_{1-6} alkyl (eg. 2-methyl or 4-methyl), C_{1-6} alkoxy (eg. 2-methoxy), trifluoromethyl (eg. 2-trifluoromethyl or 3-trifluoromethyl) or trifluoromethoxy (eg. 2-trifluoromethoxy).

When A represents a group $-Ar^2-Ar^3$, Ar^2 and Ar^3 preferably both independently represent phenyl or monocyclic heteroaryl group as defined above. Preferably A represents a group $-Ar^1$.

Most preferred $-Ar^1$ is unsubstituted phenyl.

Preferred compounds according to the invention include examples E1-E3 as shown below, or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalene-sulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

A more preferred compound according to the invention includes 3-phenylsulfonyl-8-piperazin-1-yl-quinoline or a pharmaceutically acceptable salt thereof (eg. as the hydrochloride salt), most preferably as the free base (eg. 3-phenylsulfonyl-8-piperazin-1-yl-quinoline).

It has been found that the free base of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline exists in more than one polymor-

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phic form. The present invention extends to all such forms whether in a pure polymorphic form or when admixed with any other material, such as another polymorphic form. Herein, the polymorphic forms of the free base are referred to as Form I and Form II. Each of the said forms may also be referred to herein as the free base as appropriate.

Suitably, the invention provides the free base, suitably as characterised by data provided by at least one of the following: infrared, Raman, X-ray powder diffraction or nuclear magnetic resonance and melting point data as provided herein, including partial spectral data provided herein.

In a further aspect the invention provides 3-phenylsulfonyl-8-piperazin-1-yl-quinoline Form I.

In a further aspect the invention provides 3-phenylsulfonyl-8-piperazin-1-yl-quinoline Form II.

In a particular aspect, the present invention provides 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I), characterised by

(i) an infrared spectrum substantially in accordance with FIG. 1; and/or

(ii) a Raman spectrum substantially in accordance with FIG. 2; and/or

(iii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with FIG. 3.

In a particular aspect, the present invention provides 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II), characterised by

(i) an infrared spectrum substantially in accordance with FIG. 4; and/or

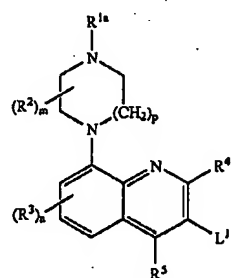
(ii) a Raman spectrum substantially in accordance with FIG. 5; and/or

(iii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with FIG. 6.

As a consequence of greater stability provided by a higher melting point, 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II) is the preferred form of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



wherein R^{1a} is as defined for R^1 or an N-protecting group, R^2 , R^3 , R^4 , R^5 , m , n and p are as defined above and L^1 is a leaving group such as iodo or trifluoromethylsulfonyloxy; with a compound of formula $A-SO_2H$, (or $A-SH$ followed by a subsequent oxidation step) wherein A is as defined above and thereafter as necessary removing an R^{1a} N-protecting group;

(b) deprotecting a compound of formula (I) which is protected; and thereafter optionally

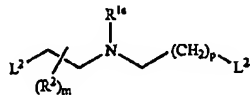
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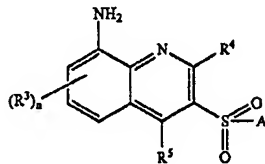
(c) interconversion to other compounds of formula (I) and/or forming a pharmaceutically acceptable salt and/or solvate.

The present invention also provides a further process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(d) reacting a compound of formula (IV)

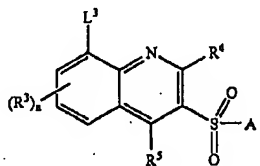


with a compound of formula (V)

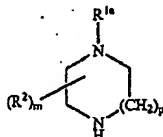


wherein R^{1a} , R^2 , R^3 , R^4 , R^5 , A , m , n and p are as defined above, and L^2 represents a suitable leaving group, such as a halogen atom and thereafter as necessary removing an R^{1a} N-protecting group; or

(e) reacting a compound of formula (VI)



with a compound of formula (VII)



wherein R^{1a} , R^2 , R^3 , R^4 , R^5 , m , n , p and A are as defined above and L^3 represents a suitable leaving group, such as a halogen atom (e.g. a bromine or iodine atom) or a trifluoromethylsulfonyloxy group, and thereafter as necessary removing an R^{1a} N-protecting group. The N-protecting group used may be any conventional group e.g. t-butyloxycarbonyl (Boc) or benzyloxycarbonyl. Further N-protecting groups which may be used include methyl.

Process (a) wherein a compound of formula (II) is reacted with a compound of formula $A-SO_2H$ typically comprises use

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of basic conditions and may be most conveniently carried out by using a suitable salt of the compound $A-SO_2H$ (e.g. the sodium salt) in an appropriate solvent such as N,N -dimethylformamide, in the presence of a transition metal salt such as copper (I) iodide.

Process (a) wherein a compound of formula (II) is reacted with a compound of formula $A-SH$ typically comprises use of basic conditions e.g. by using a suitable salt of the compound $A-SH$ (e.g. the sodium salt) in an appropriate solvent such as N,N -dimethylformamide, in the presence of a suitable metal salt such as copper (I) iodide, followed by use of a suitable oxidant such as 3-chloroperbenzoic acid, peracetic acid or potassium monopersulfate.

In processes (a) and (b), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulfonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butyloxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl ($-COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Bilman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid. A further amine protecting group includes methyl which may be removed using standard methods for N-dealkylation (e.g. 1-chloroethyl chloroformate under basic conditions followed by treatment with methanol).

Process (c) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, reductive alkylation, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, N-dealkylation of a compound of formula (I) wherein R^1 represents an alkyl group to give a compound of formula (I) wherein R^1 represents hydrogen. It will be appreciated that such interconversion may be interconversion of protected derivatives of formula (I) which may subsequently be deprotected following interconversion.

In addition, process (c) may comprise, for example, reacting a compound of formula (I), wherein R^1 represents hydrogen, with an aldehyde or ketone in the presence of a reducing agent in order to generate a compound of formula (I) where R represents C_{1-6} alkyl. This may be performed using a hydride donor agent such as sodium cyanoborohydride, sodium triacetoxyborohydride or a resin bound form of cyanoborohydride in an alcoholic solvent such as ethanol and in the presence of an acid such as acetic acid, or under conditions of catalytic hydrogenation. Alternatively, such a transformation may be carried out by reacting a compound of formula (I), wherein R^1 represents hydrogen, with a compound of formula R^1-L , wherein R^1 is as defined above and L represents a leaving group such as a halogen atom (e.g. bromine or iodine) or methylsulfonyloxy group, optionally in the presence of a suitable base such as potassium carbonate or triethylamine using an appropriate solvent such as N,N -dimethylformamide or a C_{1-6} alcohol.

Process (d) may be performed in the presence of a suitable base, such as sodium carbonate and the use of a suitable solvent such as n-butanol.

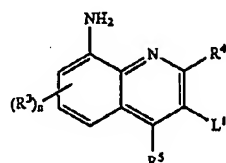
Process (e) may be performed in the presence of a palladium, nickel or copper catalyst, for example a mixture of a palladium source such as $Pd_2(dba)_3$ and a suitable ligand such as (R)-, (S)- or (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) or 2-dicyclohexylphosphanylphenyl)-dimethylamine or 1,1'-bis-diphenylphosphinoferrocene,

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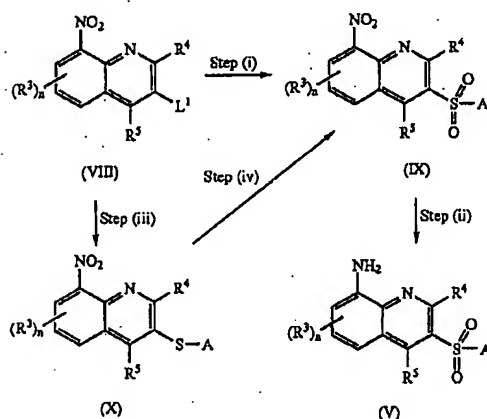
together with a suitable base such as sodium t-butoxide, in an inert solvent such as 1,4-dioxane.

Compounds of formula (II) may be prepared by reacting a compound of formula (III)



wherein R^3 , R^4 , R^5 , n and L^1 are as defined above, with a compound of formula (IV) as defined above. This process typically comprises the use of a suitable base, such as sodium carbonate and the use of a suitable solvent such as n-butanol.

Compounds of formula (V) may be prepared in accordance with the following scheme:



wherein R^3 , R^4 , R^5 , n , A and L^1 are as defined above.

Step (i) typically comprises reaction of a compound of formula (VIII) with a compound of formula $A-SO_2-M$, wherein A is as defined above and M is a metal residue such as sodium or potassium, in the presence of a copper (I) salt, e.g. copper (I) triflate or copper (I) iodide, in a suitable solvent such as anhydrous N,N-dimethylformamide or 1,4-dioxane, optionally including a ligand such as N,N'-dimethyl-ethylene-1,2-diamine.

Alternatively, the transformation shown in step (i) may be carried out using a two step procedure typically comprising steps (iii) and (iv).

Step (iii) typically comprises the reaction of a compound of formula (VIII) with a compound of formula $A-SH$, wherein A is as defined above, in the presence of a base such as sodium hydride or potassium phosphate in a suitable solvent such as anhydrous N,N-dimethylformamide or ethylene glycol, optionally in the presence of a copper (I) iodide catalyst.

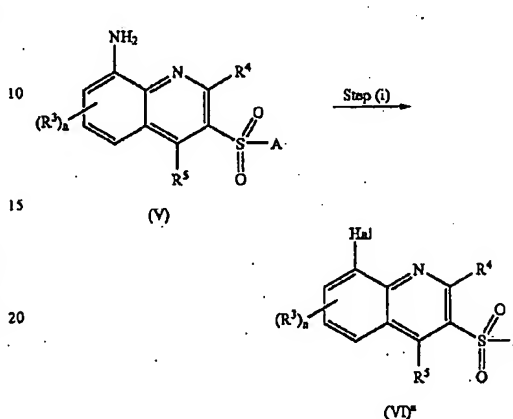
Step (iv) typically comprises oxidation using a suitable oxidant such as monomagnesium peroxyphthalate, 3-chloroperoxybenzoic acid, peracetic acid or potassium monopersulfate.

Step (ii) typically comprises the use of a suitable reducing agent, for example titanium (III) chloride, or iron powder in

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an appropriate solvent system, e.g. aqueous tetrahydrofuran and/or acetic acid, respectively.

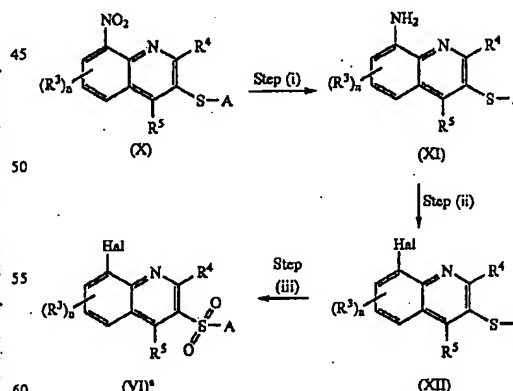
Compounds of formula (VI) wherein L^3 represents a halogen atom may be prepared in accordance with the following scheme:



wherein R^3 , R^4 , R^5 , n and A are as defined above and Hal represents a halogen atom.

Step (i) typically comprises diazotisation according to known methods (e.g. using sodium nitrite with aqueous inorganic acid as solvent, or an alkyl nitrite ester using a suitable solvent such as acetonitrile in the presence of anhydrous acid e.g. trifluoroacetic acid), followed by treatment of the resulting diazonium salt with an appropriate halide salt such as copper (I) bromide, potassium iodide or tetrabutylammonium iodide. Such a procedure may be carried out in aqueous solution or using anhydrous conditions, for example using trifluoroacetic acid as solvent.

Compounds of formula (VI) wherein L^3 represents a halogen atom may also be prepared in accordance with the following scheme:



wherein R^3 , R^4 , R^5 , A and n are as defined above and Hal represents a halogen atom.

Step (i) typically comprises the use of a suitable reducing agent such as iron powder, to give a compound of formula (XI).

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Step (ii) typically comprises a diazotisation reaction using an aqueous or non-aqueous source of nitrosonium ions as described above, followed by conversion to a halide.

Step (iii) typically comprises the use of a suitable oxidant such as monomagnesium peroxyphthalate.

Compounds of formula (VI) wherein L^3 represents a trifluoromethylsulfonyloxy group may be prepared from compounds of formula (V) as defined above, by diazotisation according to known methods, followed by heating under acidic conditions, followed by treatment with trifluoromethylsulfonic anhydride in the presence of a base, such as pyridine.

Compounds of formula (III), (IV), (VII) and (VIII) are known in the literature or can be prepared by analogous methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the 5-HT₂ receptor and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia (in particular cognitive deficits of schizophrenia), stroke and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Compounds of the invention are also expected to be of use in the treatment of obesity.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

5-HT₂ antagonists have the potential to be capable of increasing basal and learning-induced polysialylated neuron cell frequency in brain regions such as the rat medial temporal lobe and associated hippocampus, as described in International Patent Application No. PCT/EP03/00462. Thus, according to a further aspect of the present invention, we provide a method of promoting neuronal growth within the central nervous system of a mammal which comprises the step of administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical prac-

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tice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

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Description 1

3-Bromo-8-(4-methyl-piperazin-1-yl)-quinoline (D1)

bis-(2-Chloro-ethyl)-methyl-amine hydrochloride (3.7 g, 19.2 mmol) and sodium carbonate (9.0 g, 85 mmol) were added to a suspension of 3-bromo-quinolin-8-ylamine (3.9 g, 17.5 mmol) (for synthesis see Gershon et al., *Monatsh. Chem.*, 1991, 122, 935) in n-butanol (70 ml). The stirred suspension was heated at reflux for 72 h. The reaction mixture was cooled to ambient temperature, diluted with dichloromethane (300 ml) and the solution washed with water (300 ml), dried (MgSO₄) and concentrated in vacuo to an oil. The oil was purified by chromatography over silica gel eluting with a gradient of methanol/dichloromethane to afford the title compound (D1) as an oil (2.6 g, 8.5 mmol, 49%);

δ_H (CDCl₃) 2.43 (3H, s), 2.78 (4H, br s), 3.44 (4H, br s), 7.14 (1H, d, J=6.8 Hz), 7.33 (1H, d, J=7.4 Hz), 7.47 (1H, dd, J=7.8 Hz), 8.25 (1H, d, J=2.3 Hz), 8.85 (1H, d, J=2.3 Hz).

Mass Spectrum: C₁₄H₁₆BrN₃ requires 305/307; found 306/308 (MH⁺).

Description 2

3-Iodo-8-(4-methyl-piperazin-1-yl)-quinoline (D2)

A mixture of 3-bromo-8-(4-methyl-piperazin-1-yl)-quinoline (D1) (1.75 g, 5.7 mmol), copper (I) iodide (5.4 g, 28.5 mmol) and potassium iodide (9.6 g, 57.8 mmol) in hexamethylphosphoramide (20 ml) was heated in an oil bath at 150° C. for 21 h under argon. To the cooled reaction mixture was added toluene (120 ml) and 1M hydrochloric acid (120 ml) and the whole was shaken vigorously for 5 minutes. The insoluble brown solid was then collected by filtration, washed with methanol (3x40 ml) and resuspended in a mixture of dichloromethane (150 ml) and 2M sodium hydroxide (150 ml). After shaking the mixture vigorously, the insoluble material was filtered, washed with dichloromethane (2x50 ml) and discarded. The filtrate and washings were transferred to a separating funnel and the layers were separated. The aqueous phase was extracted with dichloromethane (2x100 ml) and the combined organic extracts were dried (MgSO₄) and concentrated to a brown oil (1.5 g) which was identified by NMR spectroscopy as a mixture of the title compound (D2) and 3-bromo-8-(4-methyl-piperazin-1-yl)-quinoline (D1) in a ratio of 4:1. This mixture was used directly in the next stage (see Example 1).

3-Iodo-8-(4-methyl-piperazin-1-yl)-quinoline (D2): δ_H (CDCl₃) 2.41 (3H, s), 2.76 (4H, br s), 3.42 (4H, br s), 7.14 (1H, d, J=6.8 Hz), 7.29 (1H, d, J=7.4 Hz), 7.44 (1H, dd, J=7.8 Hz), 8.47 (1H, d, J=2.3 Hz), 8.98 (1H, d, J=2.3 Hz);

Mass Spectrum: C₁₄H₁₆I₂N₃ requires 353; found 354 (MH⁺).

Description 3

3-Iodo-8-nitroquinoline (D3)

A stirred mixture of 8-nitroquinoline (100 g, 0.57 mol) in acetic acid (500 ml) was treated with N-iodosuccinimide (155 g, 0.69 mol) portionwise over 10 minutes, and warmed to 62° C. for 6 h. A further portion of N-iodosuccinimide (25 g, 0.14 mol) was introduced and the mixture stirred for a further 16 h before cooling to ambient temperature. The solvent was removed in vacuo, keeping the temperature below 35° C. The residue was dissolved in dichloromethane (2 L) and washed successively with saturated aqueous sodium bicarbonate

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solution (2x1 L), 10% aqueous sodium thiosulphate solution (1 L), water (1 L), brine (100 ml), then the organic phase was dried over magnesium sulphate. The mixture was filtered and the solvent removed to give a yellow solid which was recrystallised from ethyl acetate to give the title compound (D3) (168 g, 97%) as a yellow solid;

δ_H (CDCl₃) 7.65 (1H, app.t), 7.94 (1H, dd), 8.07 (1H, dd), 8.66 (1H, d, J=2 Hz), 9.19 (1H, d, J=2 Hz);

Mass Spectrum: C₉H₆I₂N₂ requires 300; found 301 (MH⁺).

Description 4

8-Nitro-3-phenylsulfonylquinoline (D4)

3-Iodo-8-nitroquinoline (D3) (135 g, 0.45 mol), was suspended in dimethylformamide (2.4 L) in a 5 L 3-necked flask fitted with an overhead stirrer, under an argon atmosphere. This mixture was treated successively with anhydrous sodium phenylsulfinate (99.6 g 0.608 mol), and bis-(copper (I) triflate) benzene complex (170 g, 0.338 mol). The resulting slurry was heated to 65° C. for 18 h. The mixture was cooled, filtered and the solvent evaporated in vacuo. Acetone (2.5 L) was added to the residue and the solution filtered. The filtrate was evaporated in vacuo, a further 2.5 L of acetone added and the mixture filtered again. The solvent was evaporated in vacuo and the residue dissolved in chloroform (3 L) and washed with 10% aqueous ammonia (2x2 L), and the organic phase was dried over magnesium sulphate and the solvent evaporated in vacuo. The dark brown residue was purified using a Biotage flash-150 chromatography apparatus (5 kg silica gel) eluting with hexane and increasing proportions of ethyl acetate to give the title compound (D4) (81.5 g, 58%) as a yellow solid;

δ_H (d₆-DMSO) 7.67 (2H, t), 7.57 (1H, d, 7.96 (1H, t), 8.13 (2H, d), 8.51 (1H, d), 8.59 (1H, d), 9.42 (1H, d), 9.50 (1H, d);

Mass Spectrum: C₁₅H₁₀SO₄N₂ requires 314; found 315 (MH⁺).

Description 4 (Alternative Procedure)

8-Nitro-3-phenylsulfonylquinoline (D4)

A 2L vessel was charged with 3-Iodo-8-nitroquinoline (D3) (70.8 g, 236 mmol), copper (I) iodide (2.25 g, 11.8 mmol, 5 mol %), potassium phosphate (100 g, 472 mmol, 2 eq), ethylene glycol (0.71 L, 10 vol) and benzenethiol (36.2 ml, 354 mmol). The mixture was stirred and heated at 80° C. for 3.5 hours. The reaction mixture was cooled to 20° C. then H₂O (700 ml) and dichloromethane (700 ml) were added, the mixture was stirred for 5 minutes then the lower organic layer was removed (contained solids). Charcoal (35.4 g, Norit SX) was added to the organic layer and the mixture was stirred at room temperature for 15 min then filtered through GF/F filter paper. The filter cake was rinsed with dichloromethane (140 ml) and the combined filtrate was washed with H₂O (350 ml). The resulting dichloromethane solution was added to a suspension of magnesium monoperoxyphthalic acid hexahydrate (210 g, 424 mmol, 1.8 eq) in a mixture of dichloromethane (700 ml) and methanol (140 ml) over 45 minutes maintaining 18° C.-23° C. The resulting mixture was stirred rapidly for 2.25 hours at 20° C. to 23° C., then 10% w/v aqueous sodium sulfite (700 ml) was added over 15 minutes, the mixture was separated and treated with saturated aqueous sodium bicarbonate (280 ml). The mixture was stirred for 20 min before the layers were allowed to settle. The lower organic layer was removed, washed with water (280 ml), then concentrated at atmospheric pressure to ~210 ml. The result-

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ing mixture was cooled to 0° C., stirred for 2 hrs then filtered. The filter cake was washed with cold (0-5° C.) dichloromethane (70 ml) then dried in vacuo at 25 to 40° C. to give the title compound (D4) as a light yellow solid in 64-66% yield, identical spectroscopically to that prepared by the earlier method.

Description 5

8-Amino-3-phenylsulfonylquinoline (D5)

A slurry of 8-nitro-3-phenylsulfonylquinoline (D4) (46.7 g, 172 mmol), in tetrahydrofuran (750 ml) was added to a stirred solution of 30% titanium (III) chloride in aqueous HCl (470 ml) [Supplied by BDH] cooled in an ice bath, at such a rate that the temperature was maintained below 35° C. Once the addition was completed, the solution was stirred for a further 10 minutes then water (1.5 L) was introduced and the mixture poured into a 5 L beaker. The rapidly stirred solution was treated by portionwise addition of solid potassium carbonate in order to attain pH ~8.5. EDTA (250 g, 0.86 mol) was added and followed by further potassium carbonate to maintain pH ~8.5. The mixture was extracted with dichloromethane (3x1 L) and the combined organic phase passed through a silica plug (500 g) eluting with further dichloromethane (1 L) and 10% ethyl acetate in dichloromethane (1 L). The combined organic phases were evaporated and the residue subjected to purification using Biotage Flash-75 chromatography apparatus (2 kg silica gel), eluting with dichloromethane and increasing proportions of ether to give the title compound (D5) (34.5 g, 72%) as a pale brown solid;

δ_H (CDCl₃) 5.0 (2H, br s), 7.02 (1H, dd), 7.25 (1H, dd), 7.44 (1H, t), 7.50-7.59 (3H, m), 8.00-8.40 (2H, m), 8.70 (1H, s), 0.09 (1H, s);

Mass Spectrum: C₁₅H₁₂SO₂N₂ requires 284; found 285 (MH⁺).

Description 6

8-Iodo-3-phenylsulfonylquinoline (D6)

From 8-Amino-3-phenylsulfonylquinoline (D5) in trifluoroacetic acid using n-butyl nitrite in acetonitrile followed by tetra-(n-butyl)ammonium iodide.

δ_H (CDCl₃) 7.39 (1H, t), 7.53-7.63 (3H, m), 7.96 (1H, d), 8.04 (2H, dd), 8.50 (1H, dd), 8.79 (1H, d), 9.32 (1H, d); Mass Spectrum: C₁₅H₁₀INO₂SI requires 395; found 396 (MH⁺).

Description 6 (Alternative Procedure)

8-Iodo-3-phenylsulfonylquinoline (D6)

A solution of sodium nitrite (5.44 g, 78.8 mmol, 1.2 eq) in water (125 ml, 5 vol) was added to a stirred slurry of 8-amino-3-phenylsulfonylquinoline methanesulfonic acid salt (D8) (25.0 g, 65.7 mmol) in 5M HCl (500 ml, 20 vol). The mixture was stirred at 23° to 24.5° C. for 1 hr 5 min then acetonitrile (200 ml, 8 vol) was added. After 10 min a solution of sodium iodide (14.8 g, 98.6 mmol, 1.5 eq) in water (125 ml, 5 vol) was added over 3 min, resulting in the formation of a brown mixture and the evolution of gas. The brown mixture was stirred at 25° C. to 23° C. for 1 hr 5 min then dichloromethane (500 ml, 20 vol) was added and the mixture was stirred for 5 min. The lower organic layer was removed and the aqueous layer was extracted with dichloromethane (125 ml, 5 vol). The combined organic layers were washed with 10% w/v sodium sulfite (125 ml, 5 vol) then concentrated under

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reduced pressure. The resulting mixture was filtered and the cake was washed with acetonitrile (2x25 ml) and dried in a 40° C. oven under reduced pressure to afford the title compound D6; yield 15.27 g, 59%, identical spectroscopically to that produced by the first method.

Description 7

8-(4-t-Butoxycarbonyl)piperazin-1-yl-3-phenylsulfonylquinoline (D7)

8-Iodo-3-phenylsulfonylquinoline (D6) (25.2 g, 63.6 mmol) was dissolved in dry, de-gassed dioxan (500 ml) under argon. To this solution was added sodium t-butoxide (8.56 g, 89.2 mmol) and 1-t-butyloxycarbonyl piperazine (14.2 g, 76.4 mmol) followed by a suspension of catalyst under argon. The catalyst was prepared by sonication of a mixture of tris-(dibenzylideneacetone)dipalladium(0) (1.75 g, 1.91 mmol) and 2-dicyclohexylphosphino-2'-(N,N-dimethyl amino)biphenyl (2.25 g, 5.73 mmol) in dry degassed dioxane (10 ml) for 2 minutes. This mixture was stirred at 40° C. for 5 h after which a further charge of catalyst was administered (prepared as above on half the scale) and stirring continued for 16 h at 40° C.

The mixture was filtered and the solvent removed. The residue was adsorbed onto silica and chromatographed on silica eluting with 1% methanol in dichloromethane to give the title compound (D7) (22.0 g, 76%) as a yellow solid;

δ_H (CDCl₃) 1.49 (9H, t), 3.31 (4H, m), 3.72 (4H, m), 7.25 (1H, m), 7.52 (2H, t), 7.57 (3H, m), 8.00 (2H, m), 8.76 (1H, d), 9.21 (1H, d);

Mass Spectrum: C₂₄H₂₇N₃O₄S requires 453; found 454 (MH⁺).

Description 8

8-Amino-3-phenylsulfonylquinoline methanesulfonic acid salt D8

A suspension of iron powder (26.7 g, 5 eq, 325 mesh) in THF (300 ml, 10 vol), water (30 ml, 1 vol) and acetic acid (19.2 ml, 3.5 eq) was heated to 50° C. 8-Nitro-3-phenylsulfonylquinoline (D4) (30 g, 1 wt) was added portionwise to the mixture over 30 min, keeping the temperature below 60° C. The reaction mixture was stirred at 50 to 55° C. for 60 min. Toluene (240 ml, 8 vol) was added, followed by water (60 ml, 2 vol) before cooling to 40° C. and filtering the mixture through a silica gel plug. The silica plug was washed with toluene (2x60 ml, 2 vol). The layers of the combined filtrate were separated and the organic layer concentrated in vacuo to ca 10 volumes. The reaction mixture was warmed to 77° C. then treated with methanesulfonic acid (7.42 ml, 1.2 eq) added over 15 min maintaining the temperature at 75 to 80° C. The resulting orange suspension was cooled slowly to ambient, stirred at ambient temperature for ca 2 h, then the product filtered and washed with toluene (3x60 ml). The resulting pink solid (D35) was dried in vacuo at ca 45° C. to constant weight. Yield: 34.17 g, 94%.

δ_H (d6-DMSO) 2.46 (3H, s), 7.54 (1H, d, J=8 Hz), 7.60-7.70 (3H, m), 7.70-7.75 (1H, t, J=8 Hz), 7.81 (1H, J=8 Hz), 8.13 (2H, d, J=8 Hz), 8.28 (3H, bs), 9.14 (1H, d, J=2 Hz), and 9.28 (1H, J=2 Hz).

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EXAMPLE 1

8-(4-Methyl-piperazin-1-yl)-3-phenylsulfonylquinoline (E1)

A 4:1 mixture of 3-iodo-8-(4-methyl-piperazin-1-yl)-quinoline (D2) and 3-bromo-8-(4-methyl-piperazin-1-yl)-quinoline (D1) (1.5 g), phenylsulfonic acid sodium salt, dihydrate (2.52 g, 12.6 mmol) and copper (I) iodide (2.4 g, 12.6 mmol) in N,N-dimethylformamide (25 ml) was stirred in an oil bath at 120° C. for 40 h under argon. To the reaction mixture, cooled to ambient temperature, was added 5% sodium hydrogen carbonate solution (100 ml) and dichloromethane (100 ml) with vigorous shaking. The insoluble material was filtered, washed with dichloromethane (3x20 ml) and discarded. The filtrate and washings were transferred to a separating funnel and the layers separated. The aqueous layer was extracted with dichloromethane (100 ml) and the combined organic extracts were washed with water (100 ml), dried (MgSO₄) and concentrated in vacuo to an oil (0.9 g). The oil was purified by chromatography over silica gel eluting with a gradient of methanol/dichloromethane to afford an orange oil (0.28 g, Rf 0.11, methanol/dichloromethane 1:19). This material was further purified by passage through a strong cation exchange (SCX) column eluting firstly with methanol (fractions discarded) and then with methanol/aqueous ammonia-880 (10:1) to give the title compound (E1) as an orange oil (0.152 g, 0.41 mmol, 7% over two steps);

δ_H (CDCl₃) 2.40 (3H, s), 2.72-2.76 (4H, m), 3.44 (4H, br, s), 7.25-7.27 (1H, m), 7.48-7.61 (5H, m), 7.99-8.02 (2H, m), 8.75 (1H, d, J=2.4 Hz), 9.21 (1H, d, J=2.4 Hz);

Mass Spectrum: C₂₀H₂₁N₃O₂S requires 367; found 368 (MH⁺).

EXAMPLE 1 (ALTERNATIVE PROCEDURE)

8-(4-Methyl-piperazin-1-yl)-3-phenylsulfonylquinoline (E1)

A solution of 8-amino-3-phenylsulfonylquinoline (D5) (38.8 g, 137 mmol) in n-butanol (360 ml) was treated with bis-(2-chloroethyl)-methyl-amine hydrochloride (40 g, 138 mmol) and sodium carbonate (72 g, 0.68 mol). The mixture was heated to a vigorous reflux (~100° C.) for 16 h then a further portion of bis-(2-chloroethyl)-methyl-amine hydrochloride (25 g, 86 mmol) introduced and heating continued for a further 4 h. The solution was cooled and a 1:1 mixture of saturated aqueous sodium bicarbonate and aqueous 10% sodium thiosulphate solution (2 L) added. Stirring was continued at ambient temperature for 16 h then the aqueous phase was extracted with dichloromethane (3x500 ml), the combined organic phase dried over magnesium sulphate, evaporated in vacuo and subjected to chromatography on a Biotage Flash 75 apparatus (1 kg Silica gel) to afford the title compound (E1) as the free base form (11.6 g), identical spectroscopically to that prepared by the first method.

A portion of this material was treated with 1M HCl in ether then evaporated to afford the hydrochloride salt as a yellow solid;

δ_H (CDCl₃) 2.95 (3H, d), 2.38-3.52 (4H, m), 4.01-4.06 (2H, m), 4.19-4.26 (2H, m), 7.60 (2H, t), 7.70 (1H, t), 7.96 (1H, t), 8.07 (2H, s), 8.09 (2H, s), 9.34 (1H, d), 9.63 (1H, d), 12.9 (1H, br s)

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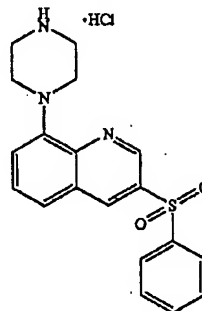
EXAMPLE 1 (ALTERNATIVE PROCEDURE)

8-(4-Methyl-piperazin-1-yl)-3-phenylsulfonylquinoline (E1)

8-Iodo-3-phenylsulfonyl-quinoline (D6) (190 mg, 0.48 mmol), N-methyl-piperazine (48 mg, 0.48 mmol), sodium tertbutoxide (65 mg, 0.68 mmol), di-palladium tetrakis-(dibenzylidene acetone) [Pd₂(dba)₃] (88 mg, 0.1 mmol) and 1,1'-diphenylphosphino ferrocene (161 mg, 0.3 mmol) were suspended in degassed dry dioxan (2 ml). The mixture was stirred under argon at 40° C. for 16 hours. The solvent was removed and the residue subjected to flash chromatography on silica gel (eluting with dichloromethane—methanol aq. ammonia) to give the title compound (E1), identical spectroscopically to that prepared by the earlier methods.

EXAMPLE 2

3-Phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E2)



A stirred solution of 8-(4-methyl-piperazin-1-yl)-3-phenylsulfonylquinoline (E1) (0.148 g, 0.4 mmol), 1-chloroethyl chloroformate (0.093 ml, 0.85 mmol) and N,N-diisopropylethylamine (0.148 ml, 0.85 mmol) in 1,2-dichloroethane (9 ml) was heated at reflux for 1.25 h under argon. The reaction mixture was cooled to ambient temperature and concentrated in vacuo to an oil. The oil was purified by chromatography over silica gel eluting with a gradient of methanol/dichloromethane, pooling fractions which contained the major component (Rf 0.9, methanol/dichloromethane 1:19). The purified material was redissolved in methanol (15 ml) and the solution was refluxed for 1 h under argon. The reaction mixture was cooled to ambient temperature and concentrated in vacuo to a solid which was stirred with diethyl ether (5 ml) and filtered to afford the title compound (E2) (0.08 g, 0.21 mmol, 51%);

δ_H (d₆-DMSO) 3.32 (4H, br s), 3.55 (4H, br s), 7.35 (1H, d, J=6.5 Hz), 7.63-7.77 (4H, m), 7.86 (1H, d, J=7.4 Hz), 8.10 (2H, m), 9.10 (1H, d, J=2.4 Hz), 9.21 (2H, s), 9.24 (1H, d, J=2.4 Hz);

Mass Spectrum: C₁₉H₁₉N₃O₂S requires 353; found 354 (MH⁺).

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EXAMPLE 2 (ALTERNATIVE PROCEDURE)

3-Phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E2)

A mixture of 8-(4-t-butoxycarbonyl)piperazin-1-yl-3-phenylsulfonylquinoline (D7), 1,4-dioxane and 4 M aqueous HCl was stirred at ambient temperature for two hours, then the solvent evaporated. The residue was co-evaporated several times from toluene and the remainder crystallised from hot ethanol to give the title compound (E2) as a yellow crystalline solid;

δ_H (d_6 -DMSO) 3.32 (4H, br s), 3.55 (4H, br s), 7.35 (1H, d, $J=6.5$ Hz), 7.63-7.77 (4H, m), 7.86 (1H, d, $J=7.4$ Hz), 8.10 (2H, m), 9.10 (1H, d, $J=2.4$ Hz), 9.21 (2H, s), 9.24 (1H, d, $J=2.4$ Hz);

Mass Spectrum: $C_{19}H_{19}N_3O_2S$ requires 353; found 354 (MH⁺);

m.p. 200° C. (phase change), 270-274° C. (decomposed)

EXAMPLE 3

3-Phenylsulfonyl-8-piperazin-1-yl-quinoline (E3), (free base form of E2)

A 100 ml three necked flask was charged with Pd₂(dba)₃ (174 mg, 0.19 mmol, 0.03 eq), 8-Iodo-3-phenylsulfonylquinoline (D6) (2.5 g, 6.33 mmol), 1,1'-bis-diphenylphosphoferrocene (316 mg, 0.57 mmol), sodium tertbutoxide (851 mg, 8.86 mmol, 1.4 eq) and piperazine (2.72 g, 31.6 mmol, 5 eq). The flask was evacuated and filled with nitrogen 4 times then anhydrous 1,4-dioxane (17.5 ml, 7 vol) was added. The mixture was stirred and heated to 40° C. for 16½ hrs.

The dark solution was allowed to cool to room temperature, dichloromethane (12.5 ml) was added and the solution was washed with H₂O (12.5 ml). The aqueous wash was extracted with dichloromethane and the combined organic layers were extracted with 5M HCl (2×12.5 ml). The combined aqueous layers were washed with (dichloromethane 2.5 ml) then transferred to a conical flask, dichloromethane (12.5 ml) was added and the flask was cooled in an ice/water bath. 10M Aqueous sodiumhydroxide (13 ml) was added whilst stirring, the mixture was then stirred at room temperature until all the solids were dissolved. The lower organic layer was removed and the aqueous layer was extracted with dichloromethane (7.5 ml), the combined organic layers were concentrated under reduce pressure to ~5 ml. Isooctane (2.5 ml) was added to the dark brown solution resulting in crystallisation, the mixture was stirred at room temp for 5 min then isooctane (22.5 ml) was added over 5 min. The mixture was aged at room temp for 1½ hrs before being cooled in an ice/water bath for 30 min, the mixture was filtered and the cake washed with isooctane (5 ml). The cake was dried under reduced pressure to give the title compound E3; yield 1.67 g, 75%.

δ_H (CDCl₃): 1.6 (1H, bs), 3.18 (4H, m), 3.34 (4H, m), 7.27 (1H, m), 7.49-7.60 (5H, m), 8.01 (2H, dd), 8.75, (1H, d), 9.21 (1H, d).

EXAMPLE 4

Crystallisation of
3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I)

3-Phenylsulfonyl-8-piperazin-1-yl-quinoline E3 (0.1 g) was dissolved in ethyl acetate (1.7 ml) with warming. On

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cooling the product crystallised as needles. Solvent was allowed to evaporate to afford the title compound in quantitative recovery. Melting point 158° C.

Characterising Data Recorded for Form I:

The infrared spectrum of the solid product was recorded using a Nicolet Avatar 360 FT-IR spectrometer fitted with a universal ATR accessory. The FT-IR spectrum (FIG. 1) shows bands at 2945, 2819, 1606, 1590, 1566, 1487, 1469, 1447, 1380, 1323, 1283, 1247, 1164, 1138, 1126, 1107, 1095, 1083, 1056, 1026, 997, 964, 949, 919, 906, 879, 859, 824, 785, 761, 723, 705 cm⁻¹

The FT-Raman spectrum was acquired using a Thermo Nicolet 960 E.S.P. spectrometer. Excitation at 1064 nm was provided by a Nd:YVO₄ laser with a power of 400 mW at the sample position. 1200 scans were recorded at 4 cm⁻¹ resolution. The FT-Raman spectrum (FIG. 2) shows bands at 215, 252, 293, 304, 315, 338, 556, 705, 858, 997, 1025, 1098, 1154, 1363, 1382, 1397, 1566, 1584, 1606 and 3059 cm⁻¹.

The X-Ray Powder Diffractogram pattern of the product (FIG. 3) was recorded using the following acquisition conditions: Unground material was packed into top-filled Si cups. Powder patterns were obtained using a Bruker D8 Advance X-Ray powder diffractometer configured with a Cu anode (40 kV, 40 mA), variable divergence slit, primary and secondary Soller slits, and a position sensitive detector. Data were acquired over the range 2-40 degrees 2-theta using a step size of 0.0145 degrees 2-theta (1 s per step). Samples were rotated during data collection. Characteristic 2θ XRPD angles are 6.84, 8.61, 10.47, 13.01, 15.11, 15.50, 16.24, 16.63, 17.20, 18.00, 19.65, 21.07, 21.66, 22.20, 22.62, 23.99, 25.61, 26.12, 26.76, 27.96, 28.86, 29.64, 30.26, 30.85, 31.31, 32.60, 33.08, 33.70, 34.35, 35.65, 36.85, 38.05 and 38.46°.

EXAMPLE 5

Crystallisation of
3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form II)

3-Phenylsulfonyl-8-piperazin-1-yl-quinoline E3 (0.5 g) was dissolved in isopropanol (5 ml) with warming. The solution was allowed to cool to ambient then stirred overnight before cooling in an ice-water bath for 15 min. The product was collected by filtration, and dried in vacuo at 50° C. to give the title compound, 371 mg, 74%. Melting point 164° C.

Characterising Data Recorded for Example 5

The infrared spectrum was recorded using a Nicolet Avatar 360 FT-IR spectrometer fitted with a universal ATR accessory. The FT-IR spectrum (FIG. 4) shows bands at: 3335, 2939, 2812, 1585, 1564, 1485, 1470, 1443, 1382, 1361, 1322, 1310, 1250, 1232, 1179, 1158, 1129, 1107, 1093, 1061, 1022, 1000, 950, 914, 862, 813, 774, 760, 727 cm⁻¹

The FT-Raman spectrum of a sample in a glass tube was acquired using a Thermo Nicolet 960 E.S.P. spectrometer. Excitation at 1064 nm was provided by a Nd:YVO₄ laser with a power of 400 mW at the sample position. 1200 scans were recorded at 4 cm⁻¹ resolution. The FT-Raman spectrum (FIG. 5) shows bands at 216, 252, 288, 617, 701, 726, 863, 1000, 1026, 1078, 1153, 1197, 1339, 1360, 1381, 1396, 1445, 1564, 1584, and 3052 cm⁻¹.

The X-Ray Powder Diffractogram pattern (FIG. 6) was recorded using the following acquisition conditions: Unground material was packed into top-filled Si cups. Powder patterns were obtained using a Bruker D8 Advance X-Ray powder diffractometer configured with a Cu anode (40 kV, 40 mA), variable divergence slit, primary and secondary Soller

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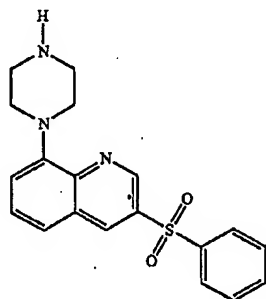
slits, and a position sensitive detector. Data were acquired over the range 2-40 degrees 2-theta using a step size of 0.0145 degrees 2-theta (1 s per step). The sample was rotated during data collection. Characteristic 2 θ XRPD angles are 9.30, 9.95, 10.99, 13.40, 14.63, 15.03, 16.04, 16.47, 17.93, 18.19, 18.73, 19.17, 20.69, 21.49, 22.12, 23.55, 24.59, 25.27, 27.03, 28.22, 28.61, 29.48, 29.81, 30.70, 32.05, 33.32, 33.95, 34.39, 34.90, 35.77, 36.25, 36.80, 37.60, 38.19, 38.70 and 39.26°.

Pharmacological Data

Compounds can be tested following the procedures outlined in WO98/27081. The compounds of Examples B1-B3 were tested and showed good affinity for the 5-HT₆ receptor, having pK_i values >8.0 at human cloned 5-HT₆ receptors.

The invention claimed is:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof.

2. A compound which is 3-phenylsulfonyl-8-piperazin-1-yl-quinoline.

3. A method of treating a cognitive memory disorder which comprises administering a therapeutically effective amount

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of the compound, or pharmaceutically acceptable salt thereof, according to claim 1 to a human in need thereof, wherein the cognitive memory disorder is selected from age related cognitive decline, mild cognitive impairment, and cognitive deficits in schizophrenia.

4. A method of treating a cognitive memory disorder which comprises administering a therapeutically effective amount of the compound according to claim 2 to a human in need thereof, wherein the cognitive memory disorder is selected from age related cognitive decline, mild cognitive impairment, and cognitive deficits in schizophrenia.

5. A crystalline form of the compound according to claim 2, wherein said crystalline form provides an X-ray powder diffraction pattern substantially in accordance with FIG. 6.

6. A crystalline form of the compound according to claim 2, wherein said crystalline form provides a Raman spectrum substantially in accordance with FIG. 5.

7. A crystalline form of the compound according to claim 2, wherein said crystalline form provides an infra red spectrum substantially in accordance with FIG. 4.

8. A method of treating Alzheimer's disease comprising administering a therapeutically effective amount of the compound, or pharmaceutically acceptable salt thereof, according to claim 1 to a human in need thereof.

9. A method of treating Alzheimer's disease comprising administering a therapeutically effective amount of the compound according to claim 2 to a human in need thereof.

10. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, according to claim 1 and a pharmaceutically acceptable carrier or excipient.

11. A pharmaceutical composition comprising the compound according to claim 2 and a pharmaceutically acceptable carrier or excipient.

* * * * *